REMARKS/ARGUMENTS

Claim 52 has been revised to feature a specific synthetic retinoid as disclosed in the specification at least on page 9, line 8. Claim 52 has also been revised to expressly indicate a correspondence between the last clause in the claim and the preamble of the claim.

Claim 61 has been revised to correct a typographical error.

Independent Claim 53 and dependent Claims 63-71 have been canceled without prejudice for re-presentation in a continuing application.

The claim revisions and cancellations are made for business reasons rather than any issue of patentability alleged in the Office Action mailed August 25, 2010. Applicants expressly reserve the right to re-present subject matter, removed from the claims by the above revisions, in a continuing application without prejudice.

No new matter has been introduced, and entry of the revised claims is respectfully requested.

No new issue for search or consideration

The above revisions to the claims leave them with the feature of a specific retinal compound which was expressly indicated as enabled in the Action mailed August 25, 2010 (see last paragraph on page 7 and first paragraph on page 8 of the Action). The specific retinal compound was also indicated as one of two fluorinated compounds indicated as "chosen by the Examiner" for search and examination (see Advisory Action mailed November 5, 2010).

Because the above indicates that the subject matter of the revised claims was searched and examined, no new issue for search or consideration is presented by the revised claims.

Claim objection

Claim 61 was objected to due to the presence of an informality, which has been obviated by the above revisions to the claim.

Alleged rejections under 35 U.S.C. § 112, first paragraph

Claims 52 and 54-62 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants have carefully reviewed the statement of this rejection and respectfully point out that the basis for this rejection is on the *in vivo* assay conditions previously featured in Claim 52.

As provided above, Claim 52 no longer includes the *in vivo* assay conditions, and so this rejection may be properly withdrawn.

Claims 53 and 63-71 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement due to the presence of "new matter." Applicants respectfully point out that these claims have been canceled without prejudice for re-presentation in a continuing application.

Therefore, this rejection may be properly withdrawn.

Claims 52 and 54-62 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement due to a lack of description of conditions encompassed by the P23H mutation. Applicants respectfully point out that these claims have been canceled without prejudice for re-presentation in a continuing application.

Therefore, this rejection may be properly withdrawn.

Claims 52-71 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly enabled only for particular retinal compounds. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of non-enablement is present.

Applicants have, however, chosen to expedite progress in the instant application by the above revisions to the claims, which now feature a single retinal compound expressly acknowledged as enabled on pages 7 and 8 of the Action mailed August 25, 2010.

Applicants' decision to revise the claims to feature 9-*cis*-10-F-retinal is not in acquiescence to the instant rejection. Indeed, no acquiescence is intended or believed to have occurred.

Instead, and contrary to the statements in the instant rejection, Applicants respectfully emphasize that enablement for the claimed invention is **not** because the Office deemed it so in the Action mailed August 25, 2010. Applicants point to well-settled legal precedent that enablement, for the claimed methods featuring the 9-*cis*-10-F-retinal compound, was present *by law* as of the filing of the instant application. The Office must grant and begin with this presumption of enablement, based on long standing legal precedent that an application's specification must be taken as presumptively enabling (see MPEP 2164.04 and the case decisions cited therein, such as *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)).

The presumption of enablement means that a skilled person in the art **has** a reasonable expectation of success in practicing the claimed invention with 9-*cis*-10-F-retinal without undue experimentation. This long standing presumption legally binds the Office and inures to the benefit of Applicants and the instant application. Importantly, the presumption is **not** dependent on knowledge in the art at the time of the invention. Instead, the Office has the burden of presenting a rebuttable *prima facie* case of non-enablement in order to challenge this presumption.

In the instant situation, there is no case of non-enablement against Claims 52 and 54-62 because of the presumption **and** because no *prima facie* case of non-enablement is present against the claims.

The presence of the presumption, however, does not mean that in the absence of the instant disclosure, the skilled person in the art at the time of the invention would have found it obvious to make and use the invention with a reasonable expectation of success. To the

contrary, the benefit of the presumption for Applicants has no legal counterpart to assist the Office, such as by lessening its burden in establishing a *prima facie* case of unpatentability.

Therefore, enablement that is present in the instant application *by law* cannot be used to support the Office's allegations of obviousness as addressed below. Instead, the Office has the burden of establishing a *prima facie* case that meets the legal requirement for a reasonable expectation of success in practicing the claimed invention with 9-*cis*-10-F-retinal.

Alleged rejections under 35 U.S.C. § 112, second paragraph

Claims 52 and 54-62 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to the term "derivative" in independent Claim 52 Applicants respectfully point out that above-revised Claim 52 no longer include use of this term, and so this rejection may be properly withdrawn.

Claims 53 and 63-71were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to a lack of description of conditions encompassed by the P23H mutation. Applicants respectfully point out that these claims have been canceled without prejudice for re-presentation in a continuing application.

Therefore, this rejection may be properly withdrawn.

Alleged rejections under 35 U.S.C. § 103

Before addressing the rejections of record, Applicants acknowledge the indication on page 16 of the Action mailed August 25, 2010 regarding the treatment of Chapple et al. ("Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa" ANCR, 3(1):12-13, 2003) as applicable as art under 35 U.S.C. § 102(a). Accordingly, Applicants expressly reserve the right to obviate the applicability of Chapple et al. as art under 35 U.S.C. § 102(a).

Claims 52-54, 60, 62-63, 69, and 71 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chapple et al. ("Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa" ANCR, 3(1):12-13, 2003) in view of Asato et al. ("Fluorinated rhodopsin analogues from 11-fluoro and 14-fluororetinal" JACS, 100(18):5957-5960, 1978). Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully traverse because no *prima facie* case of obviousness is present with respect to the above-presented claims.

As an initial matter, Applicants strongly disagree with the assertion that "Chapple already has described utilizing the 9-cis-retinal on human patients with the misfolded P23H opsin" because this statement may be mistakenly construed as indicated facts that have already occurred. The relevant portions on page 12 (right column, third paragraph) and page 13 (left column) of Chapple et al. report results with cells *in vitro*. So contrary to the instant rejection, *there are no descriptions of actual in vivo use in human patients*.

The lack of any *in vivo* data by Chapple et al. is highly significant because it means that the instant rejection also has the burden of establishing that the *in vitro* observations of Chapple et al. would be reasonably expected to occur *in vivo*, even when the conditions are modified in light of the Asato et al. document as alleged. Applicants respectfully submit that this burden has not been met in the instant rejection.

Next, Applicants point out that the Asato et al. disclosure of retinoids that bind wildtype opsin would **not** lead a skilled person to reasonably expect the same retinoids to bind P23H mutant opsin *and* prevent P23H mutant opsin aggregation *in vivo* to successfully treat human subjects as claimed. Therefore, the claims are patentable for at least this reason.

The instant rejection relies significantly on the report of Asato et al. and observations regarding fluorinated retinals *that bind wildtype opsin*. But the invention is **not** based upon the binding of a retinal to wildtype opsin. Instead, the claimed invention is based upon the binding of 9-*cis*-10-F-retinal to the P23H mutant opsin, which causes autosomal dominant retinitis pigmentosa.

The instant rejection is mistakenly based on the premise that binding of a fluorinated 9-*cis*-retinal to wildtype opsin (such as that reported by Asato et al.) indicates that the same fluorinated retinal will bind the P23H mutant opsin **and** prevent its aggregation *in vivo*. This reflects a misunderstanding because no correlation exists in the art to support the premise. The skilled person in the art knows that no correlation exists because retinitis pigmentosa (RP) caused by P23H mutant opsin is an autosomal dominant disease that has no deficiency in endogenous 11-*cis*-retinal. This means that a human subject with RP caused by P23H mutant opsin has a supply of endogenous 11-*cis*-retinal available to both the P23H mutant opsin and the wildtype opsin. But the fact that RP caused by P23H mutant opsin is an autosomal dominant disease means that the endogenous 11-*cis*-retinal **does not** bind P23H mutant opsin *to prevent its undesirable aggregation*.

The above unambiguously demonstrates that it is improper to assume that identification of a retinal as binding wildtype opsin would lead to an expectation of success in using the identified retinal to bind P23H mutant opsin **and** prevent its aggregation *in vivo*. The erroneous nature of this assumption is shown by the case of 11-*cis*-retinal, which is known to bind wildtype opsin to form visual pigment, but under endogenous, physiological conditions is unable to prevent autosomal dominant RP caused by P23H mutant opsin.

In light of the mistaken assumption at the core of the instant rejection, Applicants respectfully submit that no combination of Chapple et al. and Asato et al. can provide a skilled person with the necessary expectation of success in arriving at the claimed invention. As the Office is aware, the burden of a *prima facie* case of obviousness includes the need to demonstrate a reasonable expectation of success at the time of the invention (see MPEP 2143.02 and the case decisions cited therein). There is no presumption of a reasonable expectation of success to aid the Office. This is in contrast to the legally required presumption of enablement for the benefit of Applicants discussed above (see pages 5-6 of the instant Response).

But neither Chapple et al. nor Asato et al., whether each is taken alone or in combination, provides the necessary expectation of success. Additionally, the failure of 11-*cis*-retinal to prevent the human disease of RP caused by P23H mutant opsin demonstrates the lack of an expectation of success in selecting retinals based upon binding to wildtype opsin as

reported by Asato et al. Therefore, the instant rejection may be properly withdrawn for this reason alone.

In addition to the above, Applicants respectfully point out additional facts show that instant rejection lacks a reasonable expectation of success.

The instant rejection is based in part on the assertion that "hydrogen and fluorine are similar sterically" (see Action mailed August 25, 2010 on page 12, first paragraph) to support the premise that it would have been obvious to modify the 9-*cis*-retinal of Chapple et al. to be the fluorinated retinals of Asato et al. with retention of the results reported by Chapple et al. There are additional facts indicating the lack of a reasonable expectation of success for the fluorinated 9-*cis*-retinals of Asato et al. to bind P23H mutant opsin **and** prevent its aggregation *in vivo*.

The issue of steric similarity is limited to the fact that hydrogen and fluorine have van der Waals radii of 1.2 and 1.47 Angstroms, respectively, with a value of 1.57 Angstroms for oxygen as a point of comparison. But equally important is the fact that a skilled person in the field would be aware of other significant differences between a hydrogen moiety and a fluorine moiety. One example is the significant difference in electronegativity between hydrogen and fluorine. According to the common and widely used scale for electronegativity known as the Pauling scale, fluorine has a value of 4.0 (revised to 3.98) while hydrogen has a value of about 2.20. By way of comparison, oxygen, nitrogen, and carbon have values of 3.44, 3.04, and 2.55, respectively.

The difference in electronegativity between hydrogen and fluorine is significant in the instant situation in part because a carbon-hydrogen (C-H) bond, at the 10-position of 9-*cis*-retinal, is replaced by a carbon-fluorine (C-F) bond. This means that the respective electronegativities between the atoms in the bond go from 2.55—2.20 (in C-H) to 2.55—3.98 (in C-F). This is a dramatic shift in the character of the base 9-*cis*-retinal molecule, where an electron pair of the 10-position carbon atom (in the C-H bond) is shifted significantly toward the fluorine atom (in the C-F bond).

Additionally, and because the 10-position carbon atom is in the polyene chain of the base 9-*cis*-retinal molecule, a skilled person in the field would also expect a shift in electron

distribution in the polyene chain. The shift in electron distribution in the polyene chain is important in part because the carbon atom at the 10-position of 9-*cis*-retinal is one of the two carbon atoms in the 9-*cis* double bond. A shift in electron distribution away from the carbon atom at the 10-position (and toward the fluorine attached thereto) in 9-*cis*-10-F-retinal cannot be assumed to have insignificant effects on the 9-*cis* double bond or the retinal as a whole.

But the instant rejection is based upon an unsupported assertion that only steric similarity is needed to establish a *prima facie* case. Applicants respectfully and strongly disagree.

In light of the large change in electronegativity due to the hydrogen to fluorine modification, the Office has the burden of setting forth a *prima facie* case for why a skilled person would expect the substitution of hydrogen with fluorine to **not** impact the binding of 9-*cis*-10-F-retinal to P23H mutant opsin *and* **not** impact the prevention of P23H mutant opsin aggregation *in vivo*. Applicants respectfully submit that this burden has not been met in the instant rejection; the assertion that 9-*cis*-10-F-retinal binds wildtype opsin is insufficient to meet this burden because (as explained above with regard to 11-*cis*-retinal) there is no expectation of success based on selecting retinals that bind wildtype opsin as reported by Asato et al.

Therefore, an additional, and independent, reason is present for the absence of a *prima facie* case against the claims.

In summary, Applicants respectfully point out that the instant rejection suffers from a number of critical deficits as follows:

1) Failure to establish that the Chapple et al. *in vitro* observations with 9-*cis*-retinal would be reasonably expected *in vivo*;
2) Failure to establish a reasonable expectation of success in using the fluorinated 9-*cis*-retinal compounds of Asato et al. because their assay is only for binding to wild-type opsin rather than the P23H mutant opsin;
3) Failure to establish a reasonable expectation that even if a fluorinated 9-*cis*-retinal compound of Asato et al. binds the P23H mutant opsin, the binding would prevent deleterious aggregation of the mutant opsin *in vivo*; and

4) Failure to establish a reasonable expectation of structural and functional equivalence between 9-*cis*-retinal and 9-*cis*-10-F-retinal, in light of the significant differences in electron distribution between the two molecules, for use as featured in the claimed treatment methods.

In light of the foregoing, Applicants respectfully submit that there is no basis to conclude that a person of ordinary skill in the art, provided with the two cited documents, would have found it "obvious" to use 9-*cis*-10-F-retinal to bind P23H mutant opsin and prevent its aggregation in a manner that treats the human disease of RP caused by P23H mutant opsin.

Therefore, this rejection is misplaced and may be properly withdrawn.

Claims 55 and 64 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chapple et al. (as cited above) in view of Asato et al. (as cited above) and Grant et al. ("Treatable forms of Retinitis Pigmentosa with systemic neurological disorders"). Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully traverse because no *prima facie* case of obviousness is present with respect to the above-presented claims.

Applicants respectfully point out that Claim 64 has been canceled without prejudice and that this rejection, as applied to Claim 55, suffers from the same deficiencies in Chapple et al. and Asato et al. as explained above. Dependent Claim 55 has the same 9-*cis*-10-F-retinal feature present in revised Claim 52.

Like Chapple et al. and Asato et al., Grant et al. fail to provide a reasonable expectation of success for the use of 9-*cis*-10-F-retinal as featured in the claims.

Additionally, Grant et al. fail to teach or suggest 9-*cis*-10-F-retinal as featured in Claim 55, regardless of whether Grant et al. is taken alone or in any combination with Chapple et al. and/or Asato et al.

In light of the above, no *prima facie* case of obviousness is possible against Claim 55, and this rejection may be properly withdrawn.

Claims 56-59, 61, 65-68, and 70 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chapple et al. (as cited above) in view of Asato et al. (as cited above) in view of Lang et al. ("Ocular drug delivery conventional ocular formulations") and Geroski et al. ("Drug delivery for posterior segment eye disease") Applicants have carefully reviewed the statement of the rejection as well as the cited documents and respectfully traverse because no *prima facie* case of obviousness is present with respect to the above-presented claims.

Applicants respectfully point out that Claims 65-68 and 70 have been canceled without prejudice and that this rejection suffers from the same deficiencies in Chapple et al. and Asato et al. as explained above. Dependent Claims 56-59 and 61 have the same 9-*cis*-10-F-retinal feature present in revised Claim 52.

Like Chapple et al. and Asato et al., neither Lang et al. or Geroski et al., whether each is taken alone or in combination with any other cited document, provide a reasonable expectation of success for using 9-*cis*-10-F-retinal as featured in the claims.

Moreover, neither Lang et al. or Geroski et al. teach or suggest the 9-*cis*-10-F-retinal featured in Claims 56-59 and 61, regardless of whether Lang et al. and Geroski et al. is each taken alone or in any combination with Chapple et al. and/or Asato et al.

In light of the above, no *prima facie* case of obviousness is possible against Claims 56-59 and 61, and this rejection may be properly withdrawn.

Alleged double patenting rejections

Previous Claims 52-71 were *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting over Claim 1 of co-pending application 11/817,015. Applicants have carefully reviewed the statement of the rejection as well as the cited application and respectfully point out that it is inapplicable to the revised claims presented above.

The alleged basis for this rejection appears to be no more than an assertion that the claims in the co-pending application are thought to "encompass" the claims of the instant

application. But this assertion is made in the total absence of any demonstration that it would have been obvious to the skilled person provided with the claims of the co-pending application to arrive at the instant claims. Similarly, there is no evidence that it would have been obvious to the skilled person provided with the instant claims to arrive at the claims of the co-pending application. In light of the lack of any demonstration or evidence, no *prima facie* case of double patenting has been presented, and this rejection may be properly withdrawn.

Additionally, Applicants observe that no substantive search or examination has yet occurred in the co-pending application. Therefore, Applicants respectfully point out that with the expected allowance of the above-revised claims, this *provisional* rejection may be properly withdrawn without prejudice to either the co-pending application or the instant application.

Conclusion

In light of the foregoing, Applicants respectfully submit that the claims are allowable and urge early indication to that effect. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at number below.

Respectfully submitted,

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